REMARKS

The present invention relates to the preparation of G-CSF:polyol:oil suspensions for the sustained delivery of the G-CSF. Claims 1 and 8 have been amended above so as to specify that the compositions are prepared from a solution of G-CSF. Support for these amendments can be found throughout the specification, and no new matter is added as a result of these amendments.

PATENTABILITY ARGUMENTS

Oath/Declaration

Applicants have attempted to contact the inventor, Merrill Goldenberg, in order to execute and file a new oath/declaration which is in compliance with 37 CFR 1.67(a). Unfortunately, Applicants will not be able to obtain Mr. Goldenberg's signature until next month. Applicants will file the new oath/declaration at that time.

Objection to the Specification

The specification was objected to as relates to the use of trademarks. In this response, Applicants have amended the specification as requested by the Examiner. In view of the amendments, Applicants respectfully request that the objection be withdrawn.

35 U.S.C. §112, Second Paragraph, Rejection

In the Office Action, Claims 1-12 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Claims 1 and 9 are said to be vague and indefinite for the recitation of "polyol/thickened oil suspension" or "BAA/polyol/oil suspension". The Examiner states that is not clear if the claims encompass suspension comprising polyol and thickened oil or polyol or thickened oil.

Claim 7 is said to be indefinite for the recitation of "interferon consensus" because it was not clear if the recitation encompasses any interferon or a mixture of different types of interferons.

Claims 8, 9 and 12 are said to be confusing in their recitation of "BAA/polyol/oil". The Examiner states that is not clear if "oil" is intended to encompass "thickened oil".

Claims 2-6, 10-11 are said to be indefinite for being dependent from indefinite claims.

In this response, Applicants have canceled certain claims and amended other claims so as to specify that the biologically active agent is G-CSF, that the suspensions are prepared using a solution of G-CSF, that the suspensions contain a thickener, and that the level of said polyol in said suspension is in the range from 15%-30% by weight. In view of the arguments and amendments presented above, Applicants respectfully request that the 35 U.S.C. §112, second paragraph, rejection be withdrawn.

35 U.S.C. §102(e) Rejection

In the Office Action, Claims 1-3 and 8-12 have been rejected under 35 U.S.C. §102(e) as being anticipated by Akerblom in U.S. Patent No. 5,789,198. Akerblom teach polynucleotides which identify and encode a novel human leptin receptor-related protein (LRRP), and engineered expression vectors and host cells comprising the nucleic acid sequence encoding LRRP. In the Akerblom specification, there is general discussion regarding pharmaceutical preparations and it is disclosed that preparations for oral use may include excipients such as polyols; preparations for parenteral use may be prepared as oily suspensions; and that

certain capsule formulations may include a binder such as magnesium sterate. In view of this general disclosure, the Examiner contends that the present invention is anticipated by Akerblom.

In order to streamline prosecution of this case, Applicants have amended the claims so as to be specific to G-CSF, and so as to be directed to compositions which provide for sustained release. Akerblom provides no teaching of G-CSF or the preparation of sustained release suspension formulations as claimed in the present invention. As such, Applicants respectfully request that the 35 U.S.C. §102(e) rejection be withdrawn.

35 U.S.C. §103(a) Rejection

In the Office Action, Claims 4-7 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Akerblom in U.S. Patent No. 5,789,198, and further in view of Mitchell in U.S. Patent No. 5,411,951, Ferguson et al. in U.S. Patent No. 4,977,140 and Sims et al. (J. American Oil Society, 1977, 54, 1, pp. 4-7). The teachings of Akerblom have been described above. Mitchell in U.S. Patent No. 5,411,951 teaches bovine somatotropin suspensions comprising a biocompatible oil, and capable of providing prolonged parenteral release of drug. Ferguson et al. describe injectable sustained release formulations comprising bovine somatotropin, a wax, and an oil. Sims et al. describe addition of methionine to sunflower oil to stabilize the oil to subsequent autoxidation.

The Examiner contends that at the time the invention was made, it would have been obvious to a person of ordinary skill in the art to have included aluminum monostearate, a wax and methionine in the composition of Akerblom for any biologically active agent, including cytokines, because Akerblom clearly teaches the claimed composition with the exception of adding specific "thickeners". Applicants respectfully disagree and urge

the Examiner to reconsider the rejection, as it seems imbued with hindsight reconstruction of the prior art based on the disclosure of the present application.

As stated above, Akerblom provides only a general discussion regarding: 1) pharmaceutical compositions for oral administration may be formulated as suspensions, for ingestion by the patient; 2) that pharmaceutical formulations for oral use in form of capsules may include a coating such as glycerol and a binder such as magnesium sterate; and 3) pharmaceutical compositions for parenteral use may be prepared as oily injection suspensions. Importantly, no sustained release formulations were actually prepared by Akerblom. The Mitchell teachings involved the preparation of oil-based suspensions which were found to provide for prolonged parenteral release of zinc-associated bovine somatotropin (ZnMBS). There is discussion in Mitchell et al. regarding use of biocompatible oils composed essentially of triglycerides, i.e., long chain fatty acid esters of glycerol. Importantly, only ZnMBS powder is used in the preparation process. There is no discussion regarding the use of a polyol mixed to a ZnMBS solution and then suspended in a thickened oil to provide a sustained release composition. Ferguson et al. describe wax, oil preparations comprising bovine somatotropin. Again, the preparations utilize protein powder in the preparation of the suspensions and there is no discussion regarding the use of a polyol mixed with a protein solution and then suspended in a thickened oil to provide a sustained release composition. Sims et al. describe the use of methionine to stabilize vegetable oils. Sims et al. provide no relevant teachings as relates to the claimed invention.

The present invention was based on the surprising finding that a solution of G-CSF could be mixed with pure glycerol to form a G-CSF:glycerol suspension, and then suspended into a thickened oil mixture to provide a suspension which provides for sustained release of the G-CSF. Importantly, suspensions of G-CSF without glycerol, do not provide for sustained release. In

view of the fact that none of the cited references teach G-CSF, nor the idea that the addition of glycerol to a G-CSF solution would provide for the preparation of a sustained-release suspension as described and claimed by Applicants, Applicants respectfully request that this 35 U.S.C. §103(a) rejection be withdrawn.

35 U.S.C. §101 double patenting

Claims 1-12 have been rejected under the judicially created doctrine of double patenting over claims 1-8 of U.S. Patent No. 6,245,740. Applicant has amended the claims above so as to specify that the compositions are prepared from a solution of G-CSF. Such claims, if allowed, would not improperly extend the "right to exclude" already granted in the patent. Therefore, the Examiner is requested to hold this rejection in abeyance until the issues regarding the current claims are resolved.

CONCLUSION

In view of the foregoing, Applicant respectfully submits that the claims are in condition for allowance and earnestly request the present application pass to issue. Should any matters remain outstanding, the Examiner is encouraged to telephone Applicant's undersigned attorney at (805)-447-3011.

Respectfully submitted,

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Please send all future correspondence to:

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (amended) A sustained-release ~~suspension~~ pharmaceutical composition comprising ~~a biologically active agent (BAA)~~ granulocyte-colony stimulating factor (G-CSF) incorporated into a biocompatible polyol:~~/thickened~~ oil suspension, wherein said suspension contains a thickener, and wherein said composition is prepared by a process which comprises:

(a) mixing a solution of G-CSF in a polyol to form a G-CSF:polyol mixture;

(b) suspending said G-CSF:polyol mixture in a mixture comprising a thickened oil to form a G-CSF:polyol:oil suspension wherein the level of said polyol in said suspension is in the range from 15%-30% by weight.

2. (amended) The ~~suspension~~ composition of Claim 1 wherein said biocompatible polyol is selected from the group consisting of glycerol, erythritol, arabinose, xylose, ribose, inositol, fructose, galactose, maltose, and sucrose.

3. (amended) The ~~suspension~~ composition of Claim 1 wherein said oil is selected from the group consisting of sesame, castor, cottonseed, cannola, saffron, olive, peanut, sunflower seed, α-tocopherol, and ethyl oleate.~~; and wherein said oil contains a thickener which is selected from the group consisting of polyvalent metal salts of organic acids, oleaginous materials such as waxes and high viscosity oils, and organic or inorganic fillers such as polymers and salts.~~

4. (amended) The ~~suspension~~ composition of Claim ~~3~~ 13 wherein the thickener is aluminum monostearate.

5. (amended) The ~~suspension~~ composition of Claim ~~3~~ 13 wherein the thickener is white wax.

8. (amended) A process for preparing sustained-release pharmaceutical compositions of G-CSF:polyol:oil suspensions ~~a BAA/polyol/thickened oil sustained release suspension~~ which comprises:

~~(a) admixing a BAA in a polyol to form a BAA/polyol mixture;~~

~~(b) suspending said BAA/polyol mixture in a mixture comprising a thickened oil to form a BAA/polyol/oil suspension.~~

(a) mixing a solution of G-CSF in a polyol to form a G-CSF:polyol mixture;

(b) suspending said G-CSF:polyol mixture in a mixture comprising a thickened oil to form a G-CSF:polyol:oil suspension wherein the level of said polyol in said suspension is in the range from 15%-30% by weight.

13. (new) The composition of Claim 1 wherein the thickener is selected from the group consisting of polyvalent metal salts of organic acids, waxes and high viscosity oils.